Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson's disease: efficacy, safety and patient selection

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Summary

Long-term oral therapy with levodopa is associated with the development of motor fluctuations and dyskinesia in a large percentage of patients with Parkinson's disease (PD). Motor complications are associated with a number of non-motor symptoms and have a negative impact on disability and quality of life. There are three therapeutic options available for the management of patients at this advanced stage: high frequency deep brain stimulation, continuous subcutaneous infusion of apomorphine, and continuous intestinal infusion of levodopa/carbidopa. On the basis of published data and in consideration of the risk-benefit profile of current therapeutic strategies, we here propose an algorithm to help clinicians select the most suitable treatment option for patients with advanced PD.

KEY WORDS: continuous dopaminergic stimulation, deep brain stimulation, levodopa/carbidopa intestinal gel infusion, Parkinson's disease, patient selection

Introduction

Levodopa is the gold standard in the pharmacological treatment of Parkinson's disease (PD) (1), even though the duration of its benefit gradually shortens with disease progression (2) and its oral administration is associated with the development of disabling motor and non-motor complications in advanced disease (3). The wearing-off phenomena can be attributed to variations in levodopa plasma levels, while unpredictable ON-OFF periods may be associated with pharmacodynamic rather than pharmacokinetic mechanisms (4).

Peak-dose dyskinesias primarily involve the upper limbs and consist of painless choreiform movements that are only mildly debilitating. Diphasic dyskinesias predominate in the lower limbs, and take the form of dystonic-ballistic movements that are sometimes painful; their occurrence, both shortly after the administration of the drug, when the patient is about to enter the ON phase, as well as at the end of the dosing period before the patient enters the OFF phase, may be related to low levodopa plasma levels. OFF-phase dystonia is generally related to akinesia and may precede the clinical effects of levodopa (5). It is recognized that non-motor symptoms, especially depression, dementia and psychosis, contribute to disability in PD. Moreover, motor and non-motor fluctuations can be associated and contribute to worsening the quality of life (QoL) of both patients and their caregivers (6).

Fluctuations associated with levodopa therapy are more common than generally believed, and may sometimes occur early, shortly after the initiation of levodopa therapy (7). From an epidemiological point of view, it has been estimated that each year at least approximately 10% of patients develop motor fluctuations after starting treatment with levodopa (8). Clinical studies have shown the important role of a long-duration response (LDR) to levodopa together with the magnitude of the clinical benefit in the early phase of therapy (2). As the disease progresses, the short-duration response (SDR) becomes more prelevant and patients begin to fluctuate (2).

Despite the short half-life of levodopa (≈90 min if co-administered with carbidopa), the initial LDR can be explained by the preserved ability to store dopamine in pre-synaptic nerve terminals, thereby leading to continuous physiological release of dopamine. The progressive loss of dopaminergic neurons during the course of disease leads to reduced levodopa 'buffering' and storage capacity. As a consequence, in more advanced disease stages, dopamine release becomes generally synchronous with peripheral levodopa bioavailability (9,10). Whether or not the LDR is progressively lost as the disease progresses is still unclear; a gradual reduction in the therapeutic effects along with an increase in the magnitude of the SDR has been reported (2,11). Fluctuations become more clinically evident in the advanced stages of disease, and the degree of clinical benefits depends on the magnitude of the SDR (2,11).

Several investigations have evaluated the impact of motor complications on QoL using dedicated questionnaires (PDQ-39 or PDQ-8). In a study conducted in 143 patients, the presence of motor complications, and in particular diphasic dyskinesia, morning akinesia, end-of-dose fluctuations and unpredictable OFF periods, were associated with a significantly lower QoL total score,

with the greatest negative impact being recorded on several domains including mobility, activities of daily living (ADL), self-esteem and communication. Peak-dose dyskinesias were associated with poorer scores on mobility and emotional well-being, while cognitive decline and night-time akinesia had an impact on all the domains of the PDQ-39 questionnaire (12).
Non-motor symptoms such as anxiety, fatigue and sweating occur frequently during the OFF phase and may further worsen a patient's QoL (13). About three in 10 patients report that non-motor fluctuations are more disabling than motor variations, further underlining the importance of their early identification (3).

Therapeutic options in advanced Parkinson's disease

Treatment of patients with advanced PD remains difficult. Therapeutic options include high frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi), and continuous subcutaneous infusion of apomorphine or continuous intestinal infusion of levodopa/carbidopa.

Deep brain stimulation

Deep brain stimulation is an efficacious neurosurgical treatment for patients with advanced PD, and is associated with significant clinical benefits and improvement in QoL (14,15). Eligibility for DBS, according to the CAPSIT-PD inclusion criteria, are: age <70 years, no dementia (MMSE>25), Hoehn and Yahr (H&Y) stage ≥3, presence of motor fluctuations/dyskinesia and change in motor UPDRS score >30% between the "meds-off" and "meds-on" state (16).
Deep brain stimulation produces a marked improvement in both motor fluctuations and dyskinesias. Clinical studies have shown improvements in OFF time and reduction of dyskinesia by approximately 50%, with clinical motor improvement in 71% of patients who received DBS compared to 32% of those who received best medical therapy (17-19). Long-term studies have reported that the benefits associated with STN-DBS persist for more than 5 years, although disability may progress, reflecting degeneration in non-dopaminergic districts (20). In a recent multicentre study with a 5-/6-year follow-up of patients with advanced PD randomized to bilateral STN (STN, 35 patients) or GPi (GPi, 16 patients) DBS, both treatment groups showed a significant improvement in motor UPDRS scores (STN, $p<0.0001$, 45.4%; GPi, $p=0.008$, 20%) compared to off-stimulation, regardless of the stimulation. Dykinesias and ADL were significantly improved in both groups with fewer adverse events in the GPi-DBS group (21). However, antiparkinsonian therapy was reduced only in the STN-DBS group. Another trial confirmed that patients with PD showed similar improvements in motor function after either pallidal or subthalamic stimulation (22).
Prospective studies have shown that although the beneficial effects of DBS persist beyond 5 years, axial motor features (mainly deterioration of speech, postural impairment and freezing) and cognitive decline may occur in the long-term, after 8 years, as well as speech deterioration after an interval of 1 to 3 years following implantation (23-25).

Subcutaneous apomorphine

Apomorphine is a potent dopamine agonist with antiparkinsonian effects similar to those of levodopa. The drug is rapidly absorbed(C_{max} = 20 min) following subcutaneous administration, and has a short half-life (≈43 min) following bolus administration (26).The most common means of administration are intermittent injection and continuous subcutaneous infusion (26). Premedication with a peripheral dopamine receptor antagonist (e.g. domperidone, 10 mg 3-4 times/day for 3 days prior to infusion) may help limit adverse effects such as nausea and vomiting. Infusion of apomorphine is commonly started at 1 mg/hour and then increased by 0.5 mg/hour every 2-4 hours, depending on tolerability. Concomitant oral levodopa therapy may be reduced, and in some cases even stopped (26).
Clinical studies have consistently reported OFF-time reductions of between 50% and 80% with apomorphine infusion, although its effect on dyskinesia is less clear, and patients may still experience severe motor fluctuations (27,28). The effect on dyskinesia depends on the extent of levodopa reduction. Indications for patient selection along with efficacy and safety data for infusion of apomorphine are summarized in table I.

Duodenal administration of levodopa/carbidopa

Levodopa/carbidopa intestinal gel (LCIG) is a carboxymethylcellulose aqueous gel administered via a portable infusion pump (CADD-Legacy Duodopa, Smiths Medical, MN, USA) attached to a cassette to which a small transabdominal tube is attached. Immediate absorption of the drug through the intestinal mucosa is achieved thanks to insertion of a permanent endoscopic gastrostomy (PEG) tube, or alternatively by an internal jejunostomy tube (PEJ) (29). Administration of a gel suspension of levodopa/carbidopa directly in the duodenum using a portable pump allows continuous release of the drug at the physiological site of absorption. Duodenal infusion of LCIG bypasses gastric emptying and thus helps to avoid a potential cause of suboptimal response to levodopa (27). This leads to less variability in plasma levels of levodopa with fewer motor fluctuations compared to oral levodopa (30). Levodopa/carbidopa intestinal gel is provided in 100 ml cassettes (containing 20 mg/ml levodopa and 5 mg/ml carbidopa), which is sufficient for daily use in the vast majority of patients (29).
Clinical response and adequacy of the dose may be determined before positioning the PEG by applying a temporary nasointestinal tube. Compared to orally administered levodopa/carbidopa, pharmacokinetic studies have shown that continuous intestinal infusion provides less variability in levodopa plasma levels (31). Statistically, the coefficient of variation (for plasma concentration of levodopa) was significantly decreased with continuous infusion of levodopa/carbidopa compared to oral administration. Clinical studies have shown a good correlation between the dose of levodopa administered by infusion and an oral route. Since intestinal infusion of levodopa does not allow a reduction in the preceding daily oral dose, it is conceivable that the reduction in dyskinesia is not a consequence of the lower concentration of levodopa, but rather an effect on the central therapeutic window (32).

Levodopa/carbidopa intestinal gel is approved and marketed in the 30 countries of the European Economic Area (European Union plus Norway, Iceland and Lichtenstein) plus Croatia, Switzerland, Canada and Australia. It is under investigation for clinical use in the United States and was recognised as an orphan drug by the European Agency for the Evaluation of Medicinal Products in 2004 (29). LCIG is indicated for the treatment of advanced levodopa-responsive PD patients with severe motor fluctuations and hyper-/dyskinesia when available combinations of medicinal products have not given satisfactory results.

Overview of the effects on motor complications

OFF time reduction

The efficacy of LCIG in reducing motor fluctuations and dyskinesias in advanced PD patients has been shown by several clinical trials (29,33). The results of various clinical studies with different designs in advanced PD patients treated for periods ranging from 6 weeks to 24 months have demonstrated that compared to standard-oral therapy LCIG leads to a significant reduction in the OFF time, varying from 46% to 78% compared to baseline (30,34-39). This reduction was maintained after 24 months ($p<0.05$) (40). Table II summarizes the main findings with regard to changes in OFF time across various studies. A retrospective analysis of 65 patients with a mean follow-up period of 3.7 years also showed a benefit of LCIG infusion on freezing, which was found to be present only in 22% of patients at 1 year compared to 46% at the baseline visit (41). Moreover, a significant benefit on gait disorders (freezing, festination and postural instability) was reported in 61.4% of patients after a mean follow-up of 18 months (42).

Table I - Subcutaneous apomorphine

Patient suitability criteria	– Levodopa-responsive, idiopathic Parkinson's disease with motor fluctuations and/or dyskinesia that are not controlled with oral therapy – Availability of caregivers to provide assistance with the infusion pump
Non-suitability criteria	– Cognitive or psychiatric disturbances – Advanced age – Orthostatic hypotension – Severe hepatic, renal or cardiac comorbidity
Efficacy	– Good response for motor fluctuations – Reduced efficacy after 3 years of therapy – Limited efficacy on dyskinesia – Need to associate levodopa due to behavioural disturbances that arise from the high doses (100 mg/day) utilized. Combination therapy leads to pulsastile dopaminergic stimulation, reducing the benefits of continuous stimulation on dyskinesia – High frequency of drop-outs due to poor compliance during the first 3 months of therapy
Tolerability	– Skin nodules at the site of entry of the infusion pump – Somnolence and sedation – Nausea and vomiting – Behavioural disturbances (e.g. pathological use of internet, hypersexuality, bulimia, acute paranoia) that frequently lead to discontinuation of therapy – Need to utilize peripheral antidopaminergic drugs (e.g. domperidone) to limit nausea and vomiting

Table II - Effect of levodopa/carbidopa intestinal gel on OFF time

Authors (ref.)	Study design	N. of patients	Duration	Reduction in OFF time vs baseline
Nyholm et al., 2005 (33)	Randomized, controlled vs oral levodopa	24	3+3 weeks	Significant reduction in OFF time ($p<0.01$)
Stocchi et al., 2005 (30)	Open	6	6 months	-78% in daily hours in OFF ($p<0.001$)
Eggert et al., 2008 (35)	Open	13	12 months	-70% in daily hours in OFF
Antonini et al., 2007 (36)	Open, prospective	9	12 months	-89% in mean OFF time vs baseline ($p<0.01$)
Antonini et al., 2008 (40)	Open, prospective	22	24 months	-46% in mean OFF time (UPDRS IV) ($p<0.05$)
Santos-Garcia et al., 2011 (48)	Open, prospective	5	6 months	-91% in OFF time ($p<0.05$)
Puente et al., 2010 (38)	Open, prospective	9	18 months	Reduction in UPDRS III score, OFF from 39.7 to 29.4; ($p<0.05$)
Merola et al., 2011 (39)	Open, retrospective vs deep brain stimulation	20	15 months	Significant reduction ($p<0.05$) in time during waking day spent in OFF (item 39)

Increase in ON times without disabling dyskinesia

The previously reported retrospective study conducted in France showed clinical efficacy and tolerability in a relatively large patient cohort (42). In particular, the study included 91 patients affected by advanced PD with longstanding motor complications and a high proportion of cognitive and behavioural symptoms; the patients had a mean age of 72.7 years and a disease duration of 17 years. LCIG infusion was used in 98% of patients following failure of standard oral therapy or because of contraindication to subcutaneous apomorphine or neurosurgical treatment. Motor symptoms were evaluated in 75 patients, and in 96% of cases improvement in motor fluctuations was observed, while 95% of cases showed improvement in duration and severity of dyskinesia.
Trials in advanced PD patients treated with LCIG infusion for periods ranging from 6 months to two years have shown significant improvements in motor conditions associated with a progressive reduction of disabling dyskinesia compared to baseline. Table III shows the main results of clinical studies that considered the effect of LCIG on disabling dyskinesia (35,37,39,40, 42,43).
The trial by Merola et al. retrospectively compared 20 consecutive patients treated with LCIG infusion and 20 consecutive controls matched for age at disease onset, age at procedure, follow-up and duration of motor complications, treated with STN-DBS; the mean follow-up was 15 months. The only difference between the groups concerned neuropsychological functions, which were more impaired at baseline in the LCIG infusion group. Comparing baseline (medication-off) to follow-up values (medication-on in the LCIG infusion group; stimulation-on/medication-off in the STN-DBS group), a significant improvement in the LCIG and STN-DBS groups was observed for UPDRS-II (29% and 41%, respectively), UPDRS-III (36% and 44%, respectively) and UPDRS-IV (34% and 59%, respectively) without significant differences between the groups. STN-DBS was also associated with significant improvement compared to baseline in the duration and disability of dyskinesia, whereas less improvement was observed in the LCIG infusion group, even though the difference between groups did not reach statistical significance. A significant improvement in ADL, motor symptoms, motor complications and the percentage of the day spent in OFF was also observed in the group of patients who underwent PEG for LCIG infusion as well as in the STN-DBS group (39). STN-DBS was also associated with a significant drop in the phonemic verbal fluency score, which was more pronounced than in the LCIG infusion group.

Improvements in non-motor symptoms and QoL

Intestinal infusion of levodopa/carbidopa has significant benefits on non-motor symptoms and health-related QoL. In particular, the study by Honig et al. assessed the benefits of intestinal infusion of levodopa/carbidopa on non-motor symptoms using the NMSS scale, demonstrating an improvement in cardiovascular function ($p<0.0004$), sleep and fatigue ($p<0.0001$), attention and memory ($p<0.002$), gastrointestinal ($p<0.0003$) and urinary function ($p<0.0002$). Even the three remaining domains, namely mood and cognitive capacity, hallucinations and sexual activity, showed a trend towards improvement compared to baseline (43). Table IV summarizes the data on the effect of LCIG on non-motor symptoms and QoL from the main clinical studies considering this aspect (33,36,41-43).

Safety and tolerability

The Scandinavian Consensus Guidelines for the use of LCIG in patients with PD reported that the adverse event (AE) profile associated with the use of LCIG is the same as that for levodopa/carbidopa tablets, and further state that long-term safety follow-up studies show no unexpected side effects (<10 years) (29). However, technical problems related to the tube and gastrostomy can be observed; in fact, the infusion delivery system has been associated with procedural- and device-related technical problems in between 20% and 70% of patients (29,42,43). These complications were generally not life-threatening and did not lead to discontinuation of LCIG infusion (Table V).
In the recent trial by Merola et al., the most frequent device complication was accidental removal of the PEG tube in 55% of LCIG patients, whereas other device complications were observed with a lower frequency

Table III - Effect of levodopa/carbidopa intestinal gel on disabling dyskinesia

Authors (ref.)	Study design	N. of patients	Duration	Effect on disabling dyskinesia vs baseline
Eggert et al., 2008 (35)	Open	13	12 months	-88% on time with disabling dyskinesia ($p>0.0067$)
Antonini, et al., 2008 (40)	Open	22	24 months	-32% dyskinesia severity
Honig et al., 2009 (43)	Open	22	6 months	-67% (UPDRS dyskinesia score) ($p>0.0001$)
Devos D, 2009 (42)	Open	91	4 years	95% of patients with improved dyskinesia
Santos-Garcia et al., 2011 (48)	Open	9	6 months	-56% of patients with disabling dyskinesia ($p<0.05$) -67% diskinesia duration ($p<0.05$)
Merola et al., 2011 (39)	Open vs deep brain stimulation	20	15 months	Reduction of severity and duration of dyskinesia (items 32 and 33; p=NS vs baseline and deep brain stimulation)

[tube occlusion (5%), jejunal incarceration of the tube (5%), dislocation of the intestinal tube backwards into the stomach (10%), buried bumper syndrome (5%), and infection (15%)] (39). However, the PEG procedure itself is associated with several complications including local infections around the surgical wound, loss of weight and intestinal occlusion (39). A similar occurrence of procedural complications was reported in the French Duodopa study (technical complications in 62%) (42) and in the investigation by Nyholm et al. who reported an overall long-term rate of 1.8 per patient per year (41). In any case, it should be borne in mind that the alternative treatment for advanced patients, namely STN-DBS, can also potentially cause serious and life-threatening side effects, such as brain haemorrhage or central nervous system infections (44,45).

In general, intestinal infusion of levodopa/carbidopa is well tolerated, and the AEs associated with therapy are similar to those seen with oral levodopa and fewer than those associated with DBS (33). Table VI (over) summarises the incidence of AEs associated with continuous intestinal infusion observed in the main clinical trials (33,35,40,42).

An association between levodopa exposure and the occurrence of peripheral neuropathy in PD patients has been suggested by Toth et al. (46). In recently published papers, reduced vitamin B12 and folate levels, as well as increased total homocysteine levels, have been detected during LCIG infusion (47-49). Klostermann et al. suggested that this effect might relate to the gel formulation and potentially cause malabsorption of these nutrients (50).

Patient selection for continuous intestinal infusion of levodopa/carbidopa

On the basis of published data and considering the risk-benefit profile of the currently available therapeutic options for advanced PD, an algorithm was recently proposed specifying selection criteria and clinical charac-

Table IV - Effect of levodopa/carbidopa intestinal gel on non-motor symptoms and QoL

Author	Study design	N. of patients	Duration	Parkinson Disease Questionnaire	Quality of Life
Nyholm et al., 2005 (33)	Randomised, controlled vs levodopa	24	3+3 weeks	-28% mean change in the PDQ-39 ($p<0.01$) Significant reduction in mean scores in 7/8 domains of the PDQ-39 (mobility, $p<0.01$; daily activities, $p<0.03$; emotional well-being, $p<0.03$; self-esteem, $p<0.03$; cognitive function, $p<0.01$; communication, $p<0.03$; pain, $p<0.01$)	+7.7% in the QoL 15D ($p<0.01$)
Nyholm et al., 2008 (41)	Randomised, controlled vs Apo	4	3+3 weeks	Improvement in all domains, and in particular for stigma (-25)	Improved in 3 patients (QoL 15D), unchanged in one patient
Antonini et al., 2007 (36)	Open	9	12 months	Significant improvement in 4/8 domains of the PDQ-39 (mobility, $p<0.01$; daily activities, $p<0.01$; self-esteem, $p<0.05$ and physical discomfort, $p<0.05$)	–
Devos D, 2009 (42)	Open	91	4 years	–	93% of patients with improvement in QoL vs baseline (48% substantial improvement)
Honig et al., 2009 (43)	Open	22	6 months	Significant improvement in QoL (PDQ-8 -53%, $p=0.0003$)	–

Table V - Possible device-related complications associated with continuous intestinal infusion of levodopa/carbidopa

Gastrostomy	• Peritonitis • Acute, benign, localized infection • Localized, persistent, benign infection
Technical problems	• Pump failure • Disconnection of internal tube • Disconnection of internal tube due to severe motor dysfunction or dementia • Obstruction of internal tube • Dislocation of the internal tube and migration in the intestine

teristics of candidates, to help clinicians choose the most suitable option (27,51). A previous approach to these issues, proposed by Antonini et al., took into account factors influencing the selection of an optimal approach for continuous dopaminergic stimulation, mainly focusing on the integrity of cognitive functions and on psychological/psychiatric conditions of the patient (27). Following this scheme, Antonini and Tolosa recently published the above-mentioned algorithm, which can be used by neurologists dealing with patients showing motor complications that cannot be managed by oral medication adjustments (51). This algorithm directs the choice towards one of the three therapeutic options for advanced PD patients (subcutaneous apomorphine, DBS, and intestinal infusion of levodopa/carbidopa) mainly on the basis of patient age (greater or less than 65-70 years) and the presence of severe or mild-moderate dyskinesia. At present, on the grounds of the growing evidence on the efficacy of LCIG in dyskinesia, the use of LCIG in advanced PD patients with motor fluctuations and dyskinesia, independently of its severity, can be recommended.

In 2008, the Danish Movement Disorder Society (DANMODIS) and the Swedish Movement Disorder Society (SWEMODIS) issued joint Scandinavian guidelines for the use of LCIG infusion. These recommended that LCIG be utilized in patients with advanced PD and motor complications, who cannot be further stabilised with optimised peroral/patch treatment. They also advocate LCIG infusion for patients showing long and/or frequent OFF periods and/or severe dyskinesias, despite best peroral therapy. Unlike DBS or apomorphine, LCIG infusion can be used in elderly patients, as well as in patients with severe sleep disturbances. In these cases patients may benefit from extension of LCIG infusion to 24 hours. Slight-to-moderate dementia does not represent a contraindication for LCIG infusion (29,52).

Therefore, according to these recommendations and on the basis of literature data, it is possible to outline the clinical profile of the advanced PD patient who is a suitable candidate for intestinal infusion of levodopa/carbidopa (Table VII). Candidates for continuous intestinal infusion of levodopa/carbidopa should meet the following criteria:

– Diagnosis of PD
– Hohen&Yahr stage ≥ 3
– No age limitation
– Inadequate control of motor fluctuations and dyskinesia with oral therapy
– Responsive to levodopa
– Non-severe cognitive decline (i.e. MMSE >20)

The use of continuous intestinal infusion of levodopa/carbidopa is not recommended in patients with severe cognitive decline and/or severe dopaminergic psychosis. The presence of or a history of gastrectomy or previous gastroenteroanastomosis should be carefully assessed because this could complicate the endoscopic PEG/J implantation procedure.The availability of a reliable and responsible caregiver who can be taught to operate the pump, in terms of both dosage and maintenance, is

Table VI - Incidence of adverse events (AEs) associated with continuous intestinal infusion of levodopa/carbidopa in clinical trials

	Nyholm et al., 2005 (33) (vs conv therapy)	Antonini et al., 2008 (40)	Eggert et al., 2008 (35)	Devos, 2009 (42)
Total AEs (%)	71% (vs 76%)	–	–	–
Dyskinesia as an AE (%)	17% (vs 33%)	–	–	–
Somnolence (%)	12.5% (vs 19%)	–	–	–
Hallucinations (%)	–	–	–	–
Psychosis (%)	–	–	–	2.2%
AEs associated with the procedure (%)	–	–	69%	18% related to gastrostomy 62.6% related to technical aspects
Discontinuation due to AE (%)	–	14%	23%	–

Table VII - Effects of LCIG infusion, DBS and subcutaneous apomorphine on different PD patient characteristics

	LCIG Infusion	DBS	Apomorphine
Age > 65-70 years	+++	-	-
Mild-moderate cognitive profile	+++	++	-
Severe cognitive profile	-	-	-
Reduction of OFF time	+++	+++	+++
Reduction of dyskinesia	++	+++	-/+
Improvement of axial symptoms	-/+	-	-
Complications of procedure	+++	++	-
Adverse events profile	+	-	+++

mandatory (in the absence of an adequate caregiver, the ability of the patient to manage the pump must be verified). The contraindications for LCIG are the same as those for levodopa/carbidopa tablets as reported in the Summary of Product Characteristics for Duodopa.

Discussion

The majority of patients with advanced PD are affected by motor fluctuations and invalidating dyskinesia associated with non-motor symptoms including cognitive disturbances, depression and fatigue, leading to a substantial decline in their quality of life (12). Over time, this situation results in a progressively increasing burden on caregivers and healthcare facilities. In this context, the aim of pharmacological therapy is to provide continuous release of dopaminergic drugs, allowing steady stimulation of postsynaptic striatal receptors and a concomitant reduction of fluctuations in plasma dopamine levels. The observed variability in motor response is largely correlated with fluctuations in plasma concentrations of levodopa due to intermittent administration of the drug along with irregular gastric emptying (7).

Infusion of a levodopa/carbidopa gel (Duodopa®) via a catheter positioned in the duodenum by PEG under moderate sedation or local anaesthesia allows for more constant plasma levels of levodopa compared to oral therapy. Intestinal infusion of levodopa/carbidopa is controlled by a pump with a variable rate of infusion that allows variation of both the initial and continuous doses, with the possibility of administering an additional dose if needed. It is therefore possible to tailor the dose to meet the individual needs of the patient, which often vary during the course of the disease. The results of clinical studies on continuous intestinal infusion of levodopa/carbidopa have demonstrated that it is a valid therapeutic strategy in terms of its efficacy on both motor symptoms (reduction in OFF time, increase in ON time with disabling dyskinesia, reduction in severity of dyskinesia) (29) and non-motor symptoms (reduction in somnolence, fatigue, cardiovascular and urinary function) (36,42).

The most frequent side effects associated with intestinal infusion of levodopa/carbidopa are related to malfunction of the infusion system due to dislocation of the PEG and complications of gastrostomy such as acute or long-standing infection of the stoma (generally with a benign clinical course). Cases of peritonitis or severe drug-related psychosis are rare and may occur during the first week of therapy (38,39).

Moreover, technical issues related to the weight of the pump should be taken into consideration; furthermore, some patients, especially the elderly, will need a multi-specialist hospital team to carry out the various phases of the procedure. These include identification of candidate patients, PEG/PEJ placement, and provision of nursing assistance, both in hospital and at home.

It has been suggested that LCIG infusion may be associated with a decrease in vitamin B12 levels and folate which can potentially lead to peripheral neuropathy. As a consequence, vitamin B12 supplementation may be considered in patients treated with LCIG infusion (48). To avoid this adverse event, it is necessary to assess-gastrointestinal abnormalities and monitor vitamin levels before and during LCIG treatment, as well as perform neurophysiological screening before treatment (50). However, this topic is still controversial and further studies are necessary.

With regard to the costs involved in this treatment a study by Lowin et al. reported that LCIG infusion provides value for money in advanced patients with severe motor fluctuations when no other treatment options are effective or suitable (53). In a review by Reese et al. dopamine agonists, COMT and MAO-B inhibitors, as well as LCIG infusion and DBS, were reported to be cost-effective in the respective decision frameworks (54).

However, to date, economic evaluations of advanced therapies, rather than addressing the relative cost-effectiveness of each treatment (DBS, apomorphine or LCIG infusion), have been based on comparisons of a limited number of interventions. Indeed, the majority of existing economic evaluations in the field of advanced PD have used a relatively short-time horizon to assess cost-effectiveness (between five and ten years).

In conclusion, compared to other therapies for advanced PD, continuous intestinal infusion of levodopa/carbidopa in patients over the age of 70 years with moderate cognitive disturbances shows a rapid onset of action and is efficacious for up to 10 years on the main motor and non-motor symptoms. It also allows personalisation of therapy to individual patient needs and has a good tolerability and safety profile.The final decision on the most appropriate therapeutic option for PD patients should be based on clinical evaluation, assessment of patients' needs, as well as on the potential risk and benefits that are associated with each of the procedures here discussed.

Conflict of interest

The authors have received consultancy honoraria from Abbott.

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